Drug-induced abnormalities of potassium metabolism*

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Abstract: Pharmacotherapy has progressed rapidly over the last 20 years with the result that general practioners more and more often use drugs which may influence potassium metabolism at the kidney or gastrointestinal level, or the transmembrane transport of potassium at the cellular level. Potassium abnormalities may result in life-theatening clinical conditions. Hypokalemia is most frequently caused by renal loss of this electrolyte (thiazide, thiazide-like and loop diuretics, glucocorticoids) and the gastrointestinal tract (laxatives, diarrhea, vomiting, external fistula), and may be the result of an increased intracellular potassium influx induced by sympathicomimetics used mostly by patients with asthma, or by insulin overdosage in diabetic subjects. The leading symptoms of hypokalemia are skeletal and smooth muscle weakness and cardiac arrhythmias. Hyperkalemia may be caused by acute or end-stage renal failure, impaired tubular excretion of potassium (blockers of the renin-angiotensin-aldosterone system, nonsteroidal anti-inflammatory drugs, cyclosporine, antifungal drugs, potassium sparing diuretics), acidemia, and severe cellular injury (tumor lysis syndrome). Hyperkalemia may be the cause of severe injury of both skeletal and smooth muscle cells. The specific treatment counteracting hyperkalemia is a bolus injection of calcium salts and, when necessary, hemodialysis.

Key words: hyperkalemia, hypokalemia, potassium metabolism

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The total content of potassium in the human body is equal to 53.8 mmol/kg b.w. Approximately 10% of this amount is located in the extracellur fluid space, while the remaining 90% – in the intracellular one. Only 2% of total body potassium are dissolved in the extracellular fluid, while 8% are present in the bones. The whole amount of potassium in the human body is equal to 150 g of this element (3766 mmol) [1].

Under physiological conditions the plasma level of potassium ranges from 3.5 to 4.5 mmol/l (mean 4.5 mmol/l). In contrast to the extracellular fluid, the intracellular potassium level amounts to 90–160 mmol/l. Although no close relationship exists between potassemia and the whole body potassium content, the level of this element in blood plasma is a rough indicator of total body potassium. It is presumed that a decrease in potassemia from 4.5 to 3.5 mmol/l is equivalent to a deficiency of total potassium content of 100–200 mmol. A further decrease in potassemia by every 1 mmol/l below 3.5 mmol/l is equivalent to the reduction in total potassium of 200–300 mmol. The knowledge of this fact is of clinical importance.

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Mechanisms involved in the regulation of potassemia

The main players responsible for normokalemia are:
- the kidneys
- gastrointestinal tract
- the traumembrane transport of potassium from the extracellular fluid into the intracellular one and vice versa. This process is controlled by several hormones and activity of the sympathetic nervous system.

Every day, in adults, 600–700 mmol of potassium are filtered by the glomeruli, while only 10% of this amount (60–70 mmol) are excreted in the urine and the remaining 90% are reabsorbed by the renal tubules [1].

The following factors increase renal excretion of potassium (and thus lead to hypopotassemia):
- loop diuretics, thiazide diuretics
- increased dietary potassium intake
- activity of the tubular epithelial sodium channel (ENaC; this channel is activated by aldosterone and glucocorticoids)
- alkalosis
- increased load of the distal tubules by Na^+ and HCO_3^-.

In contrast, the following factors reduce kaliuria (which may be the reason for hyperkalemia):
- loss of active renal nephrons (acute and end-stage renal failure)

– blockers of the ENaC (potassium sparing diuretics – triamterene, amiloride, trimetoprim, cyclosporine A)
– acidosis
– congenital or acquired tubular defects (hyperkalemic types)
– insulin, aldosterone or glucocorticoid deficiency
– blockers of the renin-angiotensin-aldosterone system (RAAS): renin blockers, β-blockers, angiotensin-converting enzyme inhibitors (ACEI), AT-1-B, MR-B
– inhibitors of steroidogenesis (ketoconazole, heparin).

Under physiological conditions only 10 mmol of potassium are excreted in faeces by the gastrointestinal tract. Loss of potassium by the gastrointestinal tract may be increased by a factor of 3 to 6 in patients with diarrhea, vomiting, and those who use laxatives regularly.

Extrarenal regulation of potassemia is influenced by:
– insulin
– aldosterone
– β-adrenergic agents
– alkalosis.

All these factors stimulate the influx of potassium into cells, which decreases kalemia. In contrast to alkalosis, acidosis stimulates the transfer of potassium from the cytoplasma into the extracellular space.

Factors which stimulated the interest in potassium abnormalities

Although abnormalities in potassium metabolism have been known since more than a century ago, their detection was a difficult task because of lack of simple and reliable methods of potassium estimations. A breakthrough in this field was the introduction of flame photometry and atomic-absorptive spectrophotometry of ionselective electrodes that allowed the precise potassium estimation in blood plasma within almost few minutes, which was of paramount importance for effective treatment of hypo- and hyperkalemia. Development of precise and quick methods for potassium estimations was also triggered by the introduction of drugs strongly affecting potassium metabolism into routine practice. Among them both drugs with hypokalemic (β-adrenergic agonists, glucocorticoids, aldosterone, loop diuretics, thiazide diuretics, insulin) and hyperkalemic action (potassium sparing diuretics – trimateren, amilorid, β-blockers, renin inhibitors, ACEI, AT-1-B, MR-B, non-steroidal anti-inflammatory drugs [NSAID], cyclosporine, inhibitors of steroidogenesis – ketoconazole, heparin) should be mentioned.

Also clinical trials emphasized the need for the elaboration of reproductible methods for the potassium estimation. As it is demonstrated in the RALES study [2,3] administration of spironolactone not only had beneficial effects in patients with congestive heart failure, but also revealed an increased (by a factor of 4) number of hospitalized patients with hyperkalemia, and a sevenfold increase in mortality caused by hyperkalemia [4]. In addition, in the ALLHAT trial 10% of all treated with chlorthalidone patients showed the kalemia of ≤3.5 mmol/l [5].

Also treatment of asthmatic patients with inhaled β-sympaticomimetics and glucocorticoids essentially increased the number of patients with life-threatening hypokalemia.

Hypokalemia induced by drugs

Hypokalemia may be induced by [1,6-11]:
– loss of potassium by the kidneys (overdosage of loop or thiazide diuretics, aldosterone, gluccocorticoids, adrenocorticotropic hormone, hypomagnesemia)
– gastrointestinal tract (laxatives – bisacodyl, emetica)
– increased transfer of potassium from the extracellular into the intracellular fluid space induced by β-sympaticomimetics, insulin, aldosterone, coffeine, teophylline or refeeding).

Only rarely hypokalemia may by induced by potassium loss through the burned skin.

Clinical signs of hypokalemia [1]

The leading symptoms of hypokalemia are: weakness of skeletal, cardiae and smooth muscles (cardiac arrhythmias, rabdomyolysis, constipation and ileus), metabolic abnormalities (carbohydrate intolerance, alkalosis, hypomagnesemia), polyuria and isostenuria. Remember: Abnormalities on ECG are not a reliable marker for the severity of potassium deficiency. Electrocardiogram abnormalities are dependent not only on the extent and duration of potassium deficiency, but also upon the presence of concommitant electrolyte and acid-base abnormalities (hyponatremia, hypercalcemia, alkalosis) [12].

Therapy [11]

In hypokalemia with concommitant alkalosis, administration of potassium chloride is mandatory. In contrast, hypokalemia with acidosis is treated with potassium carbonate. It is to be remembered that a fall in kalemia from 4.5 to 3.5 mmol reflects a total body potassium deficiency of 100–150 mmol, further reduction in kalemia from 3.5 to 2.5 mmol reflects a deficiency in potassium of 300–500 mmol, while kalemia of ≤2.5 mmol/l indicates a deficiency of 500–800 mmol in this electrolyte.

Supplementation of potassium deficiency should not exced 20 mmol/h using large vascular access (*i.v.* potassium infusion is painful and may lead to blood vessel obstruction).

Drug induced hyperkalaemia [13-17]

Hyperkalemia may be spurious (caused by hemolysis, damage to leucocytes or thrombocytes), or caused by:
– increased potassium intake especially in patients with compromised excretory renal function (acute and chronic renal failure, blockade of potassium channels by drugs,

inhibitors of the RAAS, NSAID, cyclosporine) or the presence of the cardiac-renal syndrome
– impaired cellular potassium influx.

Mechanisms and drugs which increase kalemia include:
– glucorticoid and/or aldosterone deficiency
– renin deficiency (blockade of renin secretion by β-blockers, NSAID)
– inhibitors of renin (aliskiren)
– ACEI
– blockers of AT-1 receptors
– blockers of mineralocorticoid receptors (eplerenon, spironolactone)
– blockers of the ENaC (potassium sparing diuretics – triamterene, amiloride)
– inhibitors of steroidogenesis (ketoconazole, heparin)
– calcineurin immunosupressants (tacrolimus, cyclosporine A and digoxin)
– excessive plasma hyperglycemia and hyperosmolality.

Clinical presentation of hyperkalemia

Hyperkalemia may be asymptomatic or manifested by sceletal, cardiac and smooth muscle weakness, rhabdomyolysis and cardiac arrhythmias. Remember: ECG abnormalities (elongated PQ, absence of P, wide QRS, tent form of T) are unreliable predictors of sudden cardiac death.

Hyperkalemia must be confirmed by repeated potassium estimations. Acute hyperkalemia is a life-threatening condition for which immediate therapy is mandatory. It consists of the admistration of:
– 10 ml of 10% sol. of calcium gluconate *i.v.*
– infusion of 50 ml of 50% sol. of glucose with 10–20 2 IU of insulin
– *i.v.* bolus of 10 ml of 8.4% sol. of $NaHCO_3$
– administration of albuterol (by nebulizator)
– administration of potassium binding resins.

In the meantime in hyperkalemic patients hemodialysis using a dialysate potassium concentration of ≤2 mmol/l should be administered. To monitor kalemia every 30–60 minutes is mandatory. Diagnostic procedures necessary for assessment of the cause of acute hyperkalemia are performed later.

Therapy of chronic hyperkalemia is started after establishing the cause of this electrolyte abnormality, unless kalemia is not higher than 6.5 mmol/l. Patients with chronic hyperkalemia >6.5 mmol/l are treated as patients with acute hyperkalemia. That goes without saying that in patients with both acute and chronic hyperkalemia, the administration of drugs and procedures which elevate kalemia should be discontinued as soon as possible.

In patients with chronic hyperkalemia and normal excretory renal function treatment of the cause of hyperkalemia is the primary therapeutic task (supplementation of glucocorticoids in patients with Addison's disease, administration of fludrocortisone in hyporeninemic hypoaldosteronism, withdrawal of β-blokers, NSAID, potassium sparing diuretics and blockers of the RAAS respectively, treatment of hypovolemia, and reduction of dietary potassium intake).

In diabetic patients with moderate hyperkalemia (≤6.3 mmol/l) and mild renal failure, dietary restrictions of potassium intake, administration of insulin (and not oral hypoglycemic drugs), fludrocortisone and bisacodyl are highly recommended. Simultaneously, the withdrawal of RAAS blockers, NSAID and potassium sparing diuretics is mandatory.

Remember:
– More than 10% of patients treated for one year with chlorthalidon, show hypokalemia of less than 3.5 mmol/l.
– Both hypo- and hyperkalemia are life threatening settings.
– Diabetes mellitus, chronic congestive heart failure, hypovolemia, even mild chronic kidney failure and administration of some drugs (diuretics, glucocorticoids, fludrocortison, blockers of the RAAS, β-blokers, NSAID, trimetroprim, calcineurine immunosuppressants, antifungal drugs, heparins) are strong promotors of potassium abnormalities.

REFERENCES

1. Kokot F. Zaburzenia gospodarki wodno-elektrolitowej i kwasowo-zasadowej w stanach fizjologii. Warszawa, PZWL, 2005.
2. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999; 341: 709-717.
3. Effectiveness of spironolactone added to an angiotensin – converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (The Randomized Aldactone Evaluation Study [RALES]). Am J Cardiol. 1996; 76: 902-907.
4. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. N Engl J Med. 2004; 351: 543-551.
5. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT). JAMA. 2002; 288: 2981-2997.
6. Giebisch G. Renal potassium channels: function, regulation and structure. Kidney Int 2001; 60: 436–445.
7. Rastegar A, Soleimani M. Hypokalaemia and hyperkalaemia. Postgrad M J. 2001; 77: 759–764.
8. Schmiedar RE. The potential role of prorenin in diabetic nephropathy. J Hypertens. 2007; 25: 1323-1326.
9. Danser AHJ, Batenburg WW, von Esch JHM. Prorenin and the (pro) renin receptor. Nephrol Dial Transplant. 2007; 22: 1288-1292
10. Gennari FJ, Segal AS. Hyperkalemia. An adaptive response in chronic renal insufficiency. Kidney Int. 2002; 22: 1-9.
11. Kim G-H, Han JS. Therapeutic approach to hypokalaemia. Nephron. 2002; 92 (Suppl 1): 28-32.
12. Aslam S, Friedman EA, Ifudu O. Electrocardiography is unreliable in detecting potentially lethal hyperkalaemia in haemodialysis patients. Nephrol Dial Transplant. 2002; 17: 1639-1642.
13. Gross P, Pistrosch F. Hyperkalaemia: again. Nephrol Dial Transplant. 2004; 19: 2163-2166.
14. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. N Engl J Med. 2004; 351: 585-592.
15. Kim H-J, Han S-W. Therapeutic approach to hyperkalaemia. Nephron. 2002; 92 (Suppl 1): 33-40.
16. Kamel KS, Wei C. Controversial issues in the treatment of hyperkalaemia. Nephrol Dial Transp. 2003; 18: 2215-2218.
17. De Palma JR. Hyperkalemia Rx. Dialysis and Transplantation. 2004; 33: 666-683.